Antiplatelet Strategies: Evaluating Their Current Role in the Setting of Acute Coronary Syndromes

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Numerous clinical trials have established the value of antiplatelet therapies for acute coronary syndromes (ACS). Aspirin (ASA), thienopyridines (i.e., clopidogrel and ticlopidine) and GP Iib/IIia antagonists comprise the major classes of antiplatelet therapies demonstrated to be of benefit in the treatment of ACS and for the prevention of thrombotic complications of percutaneous coronary intervention (PCI). Clopidogrel is beneficial when administered before and after PCI, and is more effective when combined with either ASA or GP Iib/IIia inhibitors in preventing post-PCI complications, coronary subacute stent thrombosis, and thrombotic events in general. It is currently unclear whether a higher loading dose of clopidogrel (600 mg) is better than the standard loading dose (300 mg), how long therapy should continue, and which maintenance dose is optimal. The role of the GP Iib/IIia antagonists in ACS is less clear due to conflicting data from several studies with different patient populations. Currently, it appears that the use of GP Iib/IIia antagonists might be most beneficial in high-risk ACS patients scheduled to undergo PCI, who demonstrate non-ST-segment elevation myocardial infarction and elevated troponin levels.

Key words: catheterization/diagnostic interventional->cardiac, acute coronary syndromes->ischemic heart disease, platelets, thrombosis/hypercoagulable

Introduction

Acute coronary syndromes, one manifestation of atherothrombosis, include unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Large-scale clinical trials have established the relative value of anticoagulant and/or antiplatelet therapies for a number of conditions characterized by arterial thromboses including ACS, ischemic stroke (IS), and established peripheral artery disease (PAD). Aspirin was the first recognized antiplatelet drug based on its ability to inhibit cyclooxygenase (COX)-1 enzymatic activity. Thienopyridines (i.e., clopidogrel and ticlopidine), ASA, and GP Iib/IIia antagonists are the major classes of antiplatelet therapies found to be beneficial in the treatment of ACS, and for prevention of thrombotic complications in patients managed with PCI. The ACC/AHA practice guidelines recommend antiplatelet therapy as a cornerstone of ACS management. In this article, a review of landmark trials is undertaken, which establishes how contemporary antiplatelet therapies are used in patients with ACS.

Establishing the Benefit of Clopidogrel in Acute Coronary Syndrome Risk Reduction

The active metabolite of clopidogrel inhibits platelet activation by noncompetitively inhibiting the binding of adenosine diphosphate (ADP) to the P2Y12 receptor (ADP-receptor antagonist) that participates in the activation of the GP Iib/IIia complex. Inhibition of platelet activation via the P2Y12 signaling pathway leads to reduced activation of the GP Iib/IIia complex and thus blocks aggregation. Interference with this specific ADP-dependent step in the platelet activation pathway also restricts platelet activation by some other agonists, resulting in a further decrease in platelet recruitment and aggregation.5

Received: November 20, 2007
Accepted: November 27, 2007

DOI:10.1002/clc.20362
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The benefits of clopidogrel were established by Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Clopidogrel in Unstable angina to prevent Recurrent Events (CURE), two landmark pivotal trials that enrolled more than 31,000 patients at risk for recurrent atherothrombotic events.4,5

**Clopidogrel versus Aspirin:** The CAPRIE study evaluated 19,185 patients with atherosclerotic vascular disease, including recent myocardial infarction (MI) (with either enzyme elevation or new Q-waves on electrocardiogram [ECG]), recent IS, or established PAD.4 The primary outcome was a composite endpoint of IS, MI, or vascular death. Patients treated with clopidogrel had an annual 5.32% risk of IS, MI, or vascular death compared with 5.83% with ASA (8.7% relative risk reduction [RR] versus ASA; **p = 0.0431**).

**Establishing the Benefit of Dual Antiplatelet Therapy**

The CURE study randomized patients with UA or NSTEMI presenting within 24 hours of symptom onset to receive either clopidogrel 300 mg loading dose (followed by clopidogrel 75 mg/day) plus ASA 75 mg to 325 mg/day, or placebo plus ASA.5 The composite primary endpoint (cardiovascular [CV] death, MI, or stroke) was reduced by 20% (**p = 0.0001**) in patients who received dual antiplatelet therapy, with a clear and significant reduction in the risk of the composite endpoint that emerged by 24 h after randomization; the absolute event rate was 9.3% in the clopidogrel group and 11.4% in the placebo group after randomization; the absolute event rate was 9.3% in the clopidogrel group and 11.4% in the placebo group.

**Figure 1:** The CURE trial. Cumulative hazard rates for the first primary outcome (death from cardiovascular causes, nonfatal MI, or stroke) during the 12 months of the study. The results demonstrate the sustained effects of clopidogrel. Reproduced with permission from Yusuf S et al.5

The CURE trial support the long-term use of clopidogrel in the management of ACS, including patients who are to be medically managed.

**Use of Thienopyridines in Percutaneous Coronary Intervention**

Trials that have studied clopidogrel in the setting of PCI have typically evaluated its effectiveness for the following purposes: (1) preventing post-PCI-related complications; (2) preventing coronary stent subacute thrombosis; and (3) preventing thrombotic events in native coronary vessels. In this section, we will review a number of clinical trials in the settings of NSTEMI and STEMI, with a particular focus on clinical trials that have established the value of preprocedural and longer-term postprocedural antiplatelet therapy.

**Non-ST-Segment Elevation Myocardial Infarction**

**Establishing the value of preprocedure clopidogrel use:** Platelet activation can occur as a result of PCI in addition to postprocedure atherosclerotic plaque rupture. A substudy of 2,658 patients (21%) who underwent PCI in the CURE trial a median of 10 days after enrollment was evaluated in the Percutaneous Coronary Intervention in the Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) trial.6 The use of clopidogrel in addition to pretreatment with ASA in PCI-treated patients (**n = 1,313**) was associated with a significant reduction in the primary endpoint of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days compared with the placebo group (relative risk 0.70, **p = 0.03**) (Figure 3).6 Administration of clopidogrel therapy for a mean period of 8 months after PCI was also associated with a reduction in CV death, MI, or need for any revascularization (**p = 0.03**). Thus, this trial established that in patients with NSTEMI scheduled for PCI, clopidogrel given prior to PCI and subsequent long-term continuation may reduce both early and late major ischemic cardiovascular events in this high-risk patient group. However, the duration of pretreatment with clopidogrel (median
10 days) in PCI-CURE made the application of these results to patients undergoing urgent PCI difficult.

**Evidence to substantiate a standard 600 mg clopidogrel loading dose prior to percutaneous coronary intervention:** Platelet function studies had suggested that treatment with a higher loading dose of clopidogrel may be more effective than a 300 mg loading dose. However, the Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA-2) trial was the first randomized trial to evaluate the clinical significance of the emerging practice standard of high-dose clopidogrel pretreatment. A total of 255 patients scheduled to undergo PCI were randomized to receive a 600 mg or 300 mg loading dose of clopidogrel (in addition to ASA) administered 4–8 h prior to PCI. The primary endpoint of the 30-day occurrence of death, MI, or target-vessel revascularization occurred in 12% of those in the high-loading dose group (p = 0.041) and this effect was due entirely to protection from periprocedural MI.

In a multivariable analysis, the high-loading regimen was associated with a 50% risk reduction of periprocedural MI (odds ratio [OR], 0.48; p = 0.044). A protective effect was demonstrated in patients pretreated with statins (OR 0.28, p = 0.02); an additional risk reduction was identified in patients who were taking statins prior to intervention and received the 600 mg loading dose of clopidogrel (OR 0.20, p = 0.017). Pretreatment with a 600 mg loading dose of clopidogrel 4–8 hours before PCI did not result in postprocedural major bleeding or need for transfusion.

This study did not include STEMI patients or NSTEMI patients with elevated baseline CK-MB levels. Accordingly, although higher-risk patients needing emergency procedures would likely obtain a clinical benefit from a high-loading regimen of clopidogrel, ARMYDA-2 does not directly support the hypothesis that high-dose clopidogrel can be used as a substitute for GP IIb/IIIa inhibitors in patients with NSTEMI, but they could be used in patients with stable coronary artery disease or who are troponin-negative. However, the superior inhibition of platelet function and the results of ARMYDA-2 are factors that influenced the change in practice pattern favoring higher clopidogrel loading dosing that has been observed in recent years.

**Assessing the optimal initiation and duration of dual antiplatelet therapy:** Clopidogrel for the Reduction of Events During Observation (CREDO) was a randomized, double-blind, placebo-controlled trial involving more than 2,100 patients that evaluated the benefit of clopidogrel pretreatment (300 mg) and continuation with a maintenance dose of 75 mg/day along with ASA for 12 months after PCI (28 days of clopidogrel 75 mg/day, without a loading dose in the control group). Patients who received the loading dose and long-term clopidogrel demonstrated a 26.9% reduction in the risk of stroke, MI, or death at 1 year (p = 0.02). The benefit of extended clopidogrel therapy was consistent for each component of the composite endpoint. At 28 days post-PCI patients who received a loading dose of clopidogrel at least 6 h prior to the procedure had a 38.6% reduction in the risk of death, MI, or urgent target-vessel revascularization (p = 0.051). The CREDO trial is significant because it was the first randomized trial to assess the effect of a loading dose and duration of clopidogrel and ASA in elective PCI; its findings support administering at least 1 year of clopidogrel therapy post-PCI, and suggest a reduction of events with a longer interval between loading-dose administration and PCI.

**ST-segment Elevation Myocardial Infarction**

**Benefit of dual antiplatelet therapy in the setting of fibrinolysis:** Pharmacologic reperfusion remains the most common treatment for STEMI worldwide. Accordingly, a trial was conducted to determine the value of clopidogrel in patients with STEMI who received ASA and fibrinolytic therapy. The Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial evaluated 3,491 patients (age 18–75 years) presenting within 12 h of STEMI onset. Patients were randomly assigned to receive clopidogrel with a 300 mg loading dose or placebo; all patients also received ASA (with or without heparin), and underwent angiography within 48–192 h after initiating the study medication.

A composite primary endpoint (occluded infarct-related artery on angiography [TIMI grade of 0 or 1], death, or recurrent MI before angiography) was determined. Significantly more placebo-treated patients (21.7%) reached the composite endpoint (versus 15% in the clopidogrel group; p<0.001). By 30 days, compared with placebo, clopidogrel therapy had reduced the odds by 20% of reaching the composite endpoint of death from CV causes, recurrent MI, or recurrent ischemia leading to the need for urgent revascularization (from 14.1% to 11.6%, p = 0.03); with similar rates of major bleeding and intracranial hemorrhage in both groups. The benefit found was consistent across multiple subgroups, including those separated according to the type of fibrinolytic or heparin used.
This trial established the effectiveness by which the addition of clopidogrel to standard fibrinolytic therapy in patients under 75 years of age can improve the patency rate of the infarct-related artery and reduce ischemic complications. The CLARITY-TIMI 28 trial was particularly significant because clopidogrel’s benefit previously shown in patients with documented atherosclerosis not associated with ST-elevation was extended to patients with STEMI.

**Benefit of dual antiplatelet therapy in the setting of percutaneous coronary intervention:** A planned sub-analysis of the CLARITY-TIMI 28 trial, the PCI-CLARITY-TIMI 28 trial was conducted to determine the benefit of clopidogrel pretreatment in patients with STEMI compared with clopidogrel initiated at the time of PCI (Table 1). The composite primary endpoint of cardiovascular death, recurrent MI, or stroke from the time of PCI to 30 days after randomization was determined. Compared with no pretreatment, a significant reduction in the primary composite endpoint following PCI through 30 days post-randomization was found in patients pretreated with clopidogrel (3.6% versus 6.2%; adjusted OR, 0.54; \( p = 0.008 \)).

The clinical implications of these results are noteworthy; for every 100 patients who undergo PCI and receive clopidogrel pretreatment, approximately 2 MIs could be prevented before PCI; additionally, 2 CV deaths, MIs, or strokes could be prevented after PCI to 30 days. Only 23 patients would have to be treated with this strategy to prevent 1 CV death, MI, or stroke.

Taken together with the data from PCI-CURE and CREDO trials, PCI-CLARITY further supports the strategy of clopidogrel pretreatment in patients undergoing PCI. The broad spectrum of CAD risk for which clopidogrel pretreatment has demonstrated consistent benefit should encourage widespread incorporation of this strategy into practice in patients who are not at excessive risk of bleeding.

**Establishing a mortality benefit with the use of clopidogrel:** The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) was a large randomized, double-blind, placebo-controlled trial (n = 45,852) from 1,250 centers in China involving patients presenting within 24 h of the symptom onset of suspected STEMI. Patients were randomized to receive clopidogrel 75 mg/day (no loading dose) or placebo in combination with ASA 162 mg/day until hospital discharge (or up to 28 days). The two co-primary outcomes were: (1) a composite endpoint of death, reinfarction, or stroke; and (2) all-cause mortality during the scheduled treatment period.

COMMIT revealed the following:

- A 9% significant proportional risk reduction (PRR) (95% CI 3–14, \( p = 0.002 \)) in the composite endpoint death, reinfarction, or stroke with clopidogrel (Figure 4).
- A 7% significant PRR (95% CI, 1–13; \( p = 0.03 \)) in all-cause mortality in the ASA plus clopidogrel group compared to the ASA plus placebo group; 1,726 (7.5%) patients died in the clopidogrel group compared with 1,845 (8.1%) in the placebo group (Figure 5).
- No significant increase in the risk of bleeding during the overall treatment period.

Although no loading dose was used in this study, the findings of COMMIT are consistent with other trials adding clopidogrel to ASA in patients with ACS; however, this trial was large enough to show a mortality advantage with this strategy in suspected STEMI patients without increasing major bleeding.

**An Evaluation of Dual Antiplatelet Therapy in High-Risk Patients**

Given the benefit of dual antiplatelet therapy in patients with ACS and in those undergoing PCI, evaluating this approach as a strategy to improve outcomes in patients with established disease and multiple risk factors was the next logical step. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial randomized over 15,000 patients with clinical evidence of cardiovascular disease (CVD) or multiple risk factors to receive clopidogrel (75 mg daily) plus ASA.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel pretreatment (n = 933)</th>
<th>No pretreatment (n = 930)</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>p-value</th>
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<tr>
<td>Outcomes* before PCI</td>
<td>37 (4.0)</td>
<td>58 (6.2)</td>
<td>0.62 (0.40–0.95)</td>
<td>0.03</td>
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*Myocardial infarction or stroke. Adapted with permission from Sabatine MS et al.10
low-dose ASA (75–162 mg daily) or placebo plus low-dose ASA over 28 months. No statistically significant reduction in the risk for the first occurrence of heart attack, stroke, or cardiovascular death was observed in the clopidogrel group versus the placebo group in this broad population of patients.

Although CHARISMA was a negative trial with respect to the primary efficacy endpoint in the overall population, patients enrolled with established atherothrombotic disease (also referred to as secondary prevention) who received dual antiplatelet therapy, had a reduction in relative risk of a recurrent MI, stroke, or cardiovascular death compared to patients receiving placebo and ASA (6.9% with clopidogrel versus 7.9% with placebo; RR, 0.88; 95% CI, 0.77–0.998; p = 0.046). A subsequent subgroup analysis of patients enrolled with prior MI, prior ischemic stroke, or symptomatic peripheral arterial disease showed a larger possible benefit (7.3% with clopidogrel versus 8.8% with placebo (hazard ratio, 0.83; 95% CI, 0.72–0.96; p = 0.01). Future trials will need to confirm whether intensification of chronic antithrombotic therapy beyond ASA alone in these types of patients is truly useful.

Additionally, asymptomatic patients in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (those with multiple risk factors without documented cardiovascular disease, such as diabetic patients) who received dual platelet inhibition had no benefit, but did have an increased risk of bleeding. Therefore, dual antiplatelet therapy would not be recommended in such patients, even though they are at high risk for future ischemic events. It is unlikely that in a primary prevention population more than ASA alone will be useful in regards to antithrombotic therapy.

Evaluating the Role of Glycoprotein IIb/IIIa Antagonists in Acute Coronary Syndrome Management

The GP IIb/IIIa receptors are members of the integrin family of adhesion receptors. Once activated, these receptors are able to bind adhesion proteins involved in platelet aggregation, such as von Willebrand factor (vWF) and fibrinogen. Inhibition of the platelet GP IIb/IIIa receptor in the treatment of patients with ACS has been well-studied with placebo-controlled trials completed in more than 30,000 patients. A meta-analysis on the use of GP IIb/IIIa inhibitors in ACS demonstrated a 1% absolute benefit in preventing thrombotic events compared with placebo (10.8% versus 11.8%; p = 0.015). However, an absolute 1% increase in major bleeding was also observed in GP IIb/IIIa-treated patients, suggesting the need to identify certain subgroups of patients with ACS who would be more likely to achieve benefit from these compounds.

Determining the benefit of glycoprotein IIb/IIIa receptor antagonists in unstable angina and non-ST-segment elevated myocardial infarction: The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial was a randomized, double-blind study that assessed whether
the nonpeptide GP IIb/IIIa receptor antagonist tirofiban, when compared to unfractionated heparin, improved unstable clinical outcomes in 3,232 patients with UA already receiving ASA. The occurrence of the composite endpoint (death, MI, or refractory ischemia at 48 h) was lower in the tirofiban group compared with unfractionated heparin (UFH)-treated patients (3.8%, versus 5.6%, respectively; risk ratio [RR], 0.67; \( p = 0.01 \)). The PRISM-Patients Limited by Unstable Signs and Symptoms (PLUS) study differed from PRISM in its inclusion of a third treatment arm of patients who received tirofiban and heparin and patients with NSTEMI; a majority of patients were receiving UFH at the time of randomization. The tirofiban-only arm was discontinued early because of an increase in deaths at day 7. The frequency of the composite primary endpoint (death, MI, or refractory ischemia) at 7 days was lower among the patients who received tirofiban plus UFH than among those who received UFH alone (12.9% versus 17.9%, respectively; RR, 0.68; \( p = 0.004 \)). At 30 days and at 6 months, the rate of the composite endpoint in the tirofiban plus UFH group was also lower than that in the UFH-only group (18.5% versus 22.3% at 30 days and 27.7% versus 32.1% at 6 months, respectively; \( p = 0.03 \) and \( p = 0.02 \), respectively). The PRISM and PRISM-PLUS trials established the initial value of tirofiban in patients with UA and NSTEMI.

**Evaluation of abciximab in acute coronary syndromes:** At least one randomized trial had demonstrated the beneficial effects of GP IIb/IIIa inhibitors in patients with refractory angina who underwent PCI\(^2\) and with tirofiban in patients who underwent early revascularization;\(^2\) however, no benefit was observed with the monoclonal antibody and platelet GP IIb/IIIa receptor inhibitor abciximab after 30 days follow-up in the Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndrome study (GUSTO IV-ACS) trial. This study evaluated the effects of abciximab in NSTEMI patients not scheduled for PTCA or CABG. Patients (\( n = 7,800 \)) were randomized to receive either abciximab bolus and 24-hour infusion, abciximab bolus and 48-hour infusion, or matching placebo.\(^2\) At 1 year, no survival benefit was demonstrated to be associated with abciximab. Moreover, a higher mortality rate was demonstrated in patients who were troponin-negative or had elevated C-reactive protein levels (\( p = 0.02 \) and \( p = 0.04 \), respectively).\(^2\) A meta-analysis of 6 large randomized trials of patients with ACS not scheduled to undergo early revascularization (including 30-day death or MI results from GUSTO IV-ACS) found the largest treatment benefit for patients with elevated troponin levels.\(^2\)

**Comparison of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention:** Although a number of trials conducted with GP IIb/IIIa inhibitors in the setting of PCI had demonstrated reductions in the 30-day composite endpoint of death, MI, and need for urgent revascularization, a direct comparison between the relative efficacy of abciximab and tirofiban had not been undertaken. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) evaluated whether tirofiban and abciximab provide similar efficacy outcomes among patients undergoing non-emergent, stent-based PCI in an international multicenter study in 4,809 patients randomly assigned a bolus and infusion of tirofiban or abciximab. At 30 days, the composite primary endpoint of death, MI, and urgent target-vessel revascularization had occurred more frequently among tirofiban-treated patients compared with those who received abciximab (7.6% versus 6.0%; \( p = 0.038 \)).\(^2\)

**Evaluating the necessity of abciximab with increased clopidogrel loading doses:** Evidence from PCI-CURE and CREDO supports the practice of clopidogrel pretreatment to prevent post-PCI complications. The Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) trial which used a 600-mg loading dose of clopidogrel, demonstrated good tolerability and an extremely low occurrence of early complications.\(^2\) Given the recent shift in practice toward routine preprocedural use of clopidogrel 600 mg loading doses, the ISAR-REACT-2 trial sought to determine whether the antiplatelet effect provided by clopidogrel 600 mg loading doses obviates the need for GP IIb/IIIa inhibitors in high-risk patients with ACS who undergo PCI. The ISAR-REACT-2 trial was an international, multicenter, double-blind, placebo-controlled trial that randomized patients (\( n = 2,022 \)) with NSTEMI undergoing PCI to receive either of the following: abciximab (0.25 mg/kg, followed by a 0.125 \( \mu \)g/kg/m infusion for 12 hours, plus UFH) or placebo plus UFH bolus, 140 U/kg. All patients received clopidogrel 600 mg at least 2 hours prior to PCI and ASA 500 mg (oral or IV). Although the primary composite endpoint (death, MI, or urgent target-vessel revascularization occurring within 30 days after randomization) occurred in 8.9% of abciximab-treated patients compared with 11.9% placebo-treated patients (Figure 6A) (RR, 0.75; \( p = 0.03 \)), there was no statistically significant difference among patients without elevated troponin levels (Figure 6B).\(^2\) There was a 29% reduction in this endpoint in patients with elevated troponin levels. These results indicate that the role of GP IIb/IIIa antagonists with clopidogrel pretreatment appears to be in higher-risk NSTEMI patients with elevated troponin levels.

**Conclusion**
The benefit of clopidogrel in ACS was established by two landmark studies: CAPRIE and CURE. The use of clopidogrel is now a key component of treatment strategies used in the management of ACS, particularly...
for patients who undergo PCI and require peri- and postprocedural thrombus prevention. The role of the GP IIb/IIIa antagonists in ACS is less well characterized, based on the conflicting results of several studies evaluating different patient populations. At this time, it appears that the use of GP IIb/IIIa antagonists might be most beneficial in high-risk patients with NSTE MI and elevated troponin levels who are scheduled to undergo PCI. Novel antiplatelet approaches and future clinical trials will characterize further how to maximize the benefit of antiplatelet therapy in the setting of ACS and solve currently unmet clinical needs in this area, determine what role these agents have in thrombotic prevention, and which patient populations will benefit the most.

References


